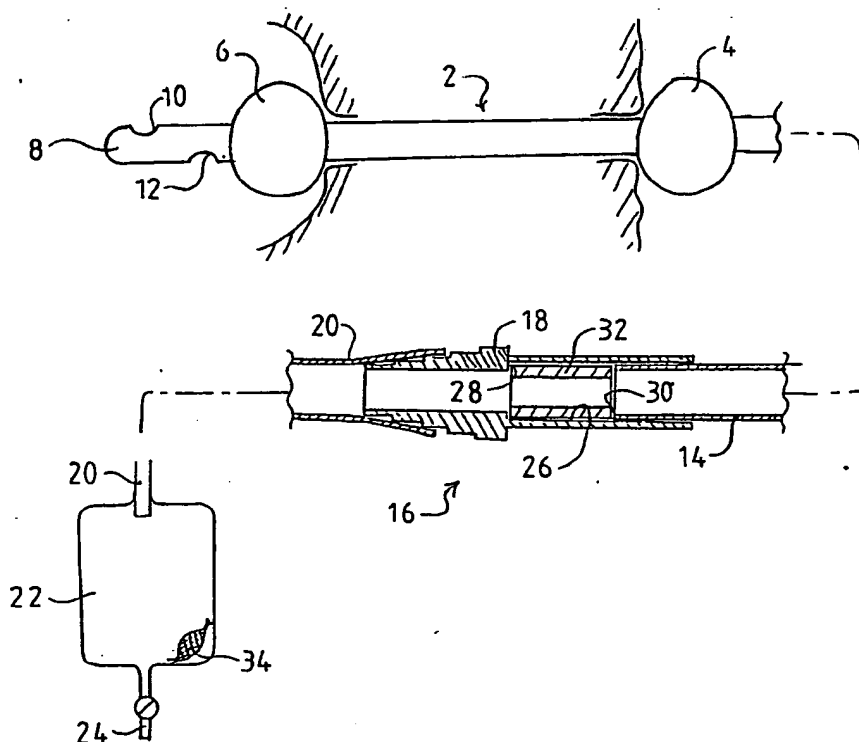




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/GB88/00701 (22) International Filing Date: 26 August 1988 (26.08.88) (31) Priority Application Number: 8720502 (32) Priority Date: 29 August 1987 (29.08.87) (33) Priority Country: GB (71) Applicant (for all designated States except US): GIL-TECH LIMITED [GB/GB]; 11/12 North Harbour, Industrial Estate, Ayr KA8 8AA (GB). (72) Inventor; and (75) Inventor/Applicant (for US only) : GILCHRIST, Thomas [GB/GB]; 67 Midton Road, Ayr (GB). (74) Agent: MURGITROYD AND COMPANY; Mitchell House, 333 Bath Street, Glasgow G2 4ER (GB).		(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i>

(54) Title: APPARATUS FOR ANTIMICROBIAL USE**(57) Abstract**

Apparatus for use in fluid flow lines to or from a living body in order to reduce the incidence or growth of bacteria comprising in the flow line a connecting member (16) which includes water-soluble silver impregnated glass (32), whereby the glass undergoes slow dissolution with concomitant release of silver into the fluid. The silver has antibacterial or bacterial static properties.

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Apparatus for antimicrobial use.

This invention relates to an antimicrobial composition for use in medicine. The invention also relates to a device
5 for use in medicine, which embodies the said composition and to a method of inhibiting or combating infection.

The antimicrobial action of silver ions is well known as are pharmaceutical formulations containing silver salts as
10 active principle. Perhaps the best known example of such materials is silver sulphadiazine. However, silver nitrate and silver allantoinate are also used as antimicrobials.

For protracted protection against infection it is desirable
15 that the release of the silver ion be sustained over an extended period of time.

It is known that certain glasses, in which the usual glass former, silicon dioxide, of traditional glasses is replaced
20 with phosphorus pentoxide as the glass former, are soluble in water and body fluids. The rate of dissolution is controlled largely by the addition of glass modifiers such as calcium and magnesium oxide. In simple terms, the
greater the concentration of the modifier the slower is the
25 rate of dissolution. The rates of dissolution which can be

imparted to the glasses may range from minutes to months or even to several years. It is known to include in such compositions quantities of trace elements such as copper, cobalt and selenium which will be released from the glass as it slowly dissolves over the selected period of time.

The use of water-soluble glasses has been described for a variety of purposes in the literature. For example, UK Patent Specifications numbers 1,565,906, 2,079,152, 2,077,585 and 2,146,531 describe the gradual dissolution of the glasses as providing a means of controlled release of drugs, hormones, fungicides, insecticides, spermicides and other agents with which the glasses have been impregnated. The glasses are used for example in the form of an implant or bolus.

UK Patent Specification number 2,030,559 describes the use of selenium-impregnated water-soluble glass for providing controlled release of the selenium as a trace element into cattle and sheep, the glass being applied as a subcutaneous insert. UK Patent Specification number 2,037,735 also describes a subcutaneous implant of water-soluble glass, and in this case the glass is impregnated with copper; minor quantities of trace elements such as boron, arsenic, iodine, manganese, chromium, silver, gold and gallium may also be included.

Water-soluble glass has also been proposed for use in prosthetics, for example in UK Patent Specification number 2,099,702, and for use in anticorrosive paints, as described in UK Patent Specification number 2,062,612. Further the literature provides for the use of such glasses in the controlled release of ferrous and ferric ions into the human or animal body by ingestion or implantation of the glass (UK Patent Specification number 2,081,703), and for the use of

glasses in the controlled release of ions such as lithium, sodium, potassium, caesium, rubidium, polyphosphate, calcium and aluminium to patients by inclusion of the glass in a drip feed line (UK Patent Specification number 2,057,420).

5

According to the present invention there is provided apparatus for antimicrobial use in passage of fluid to or from a living body, the apparatus comprising a conduit for insertion into the body, a reservoir for fluid and a
10 connector member for connecting said conduit to said reservoir external of the body, wherein said connector member includes a water-soluble glass impregnated with elemental silver or a compound of silver, said water-soluble glass defining at least a part of a passageway for fluid to
15 flow between the reservoir and the conduit.

The apparatus of the present invention preferably contains the impregnated water-soluble glass at a site at which bacteria can be introduced or increased in number, and the
20 bacteriostatic or bactericidal properties of the silver has the effect of containing or reducing the risk of infection in the body. The connector member may comprise a first portion having an end adapted for connection with said conduit and a second portion having an end adapted for
25 connection with said reservoir, the first and second portions being releasably secured together to define a fluid passageway between the reservoir and the conduit and at least one of the first and second portions having an internal lining of said impregnated water-soluble glass.
30 The internal lining may be retained between spaced shoulders on the first or second portion, so that when the portions are separated the lining is held in position until re-connection is made.

35 The connector member may be in the form of a fitting which

connects together upstream and downstream tubing, each of the first and second portions of the connector being disposed at an end of the respective tubing. If it becomes necessary to disconnect the tubing remote from the patient, for example to replace a full reservoir of fluid drained from the patient with an empty one, or to replace an empty reservoir of fluid delivered to the patient with a full one, the connector can be broken and the silver reduces the danger of infection to the patient through ingress of bacteria.

The connector member may consist of or include a length of tubing, for example of plastics material, rubber or silicone rubber, in which the impregnated water-soluble glass is dispersed so that the silver is released from the tubing wall.

The reservoir may also contain impregnated water-soluble glass, especially in the case where fluid is being drained from the patient, for example in urine drainage systems. During collection of the urine in the reservoir in conventional systems bacteria multiply and there is a risk that they may migrate along the drainage tubing to the patient, thereby increasing the incidence of bacteria and producing urinary tract infection. Inclusion in the reservoir of an apertured container in which silver-impregnated water-soluble glass is disposed prevents the multiplication of bacteria in the reservoir and therefore reduces the infection risk. A preferable form of container has been found to be a flexible braided polyester sleeve closed at each end to form an elongate pouch and containing granules of the glass. This system also protects nursing staff, who are required to replace full reservoirs, and/or to drain off urine from full reservoirs, by preventing proliferation of bacteria in the urine.

The apparatus of this invention may be used for example in urine drainage systems, post-surgical drainage systems, cannula systems and renal and peritoneal dialysis systems.

5 The present invention also provides a connector member having an inlet and an outlet and having walling defining a through passageway for flow of liquid from the inlet to the outlet, at least a part of said walling being formed of water-soluble glass impregnated with elemental silver or a
10 compound of silver.

The optimum rate of release of silver ions into an aqueous environment may be selected by circumstances and particularly by the specific function of the released
15 silver. In some cases, the required rate of release may be such that all of the silver added to the system is released in a short period of hours or days and in other applications it may be that the total silver be released slowly at a substantially uniform rate over a period extending to months
20 or even years. In particular cases there may be additional requirements, for example it may be desirable that no residue remains after the source of the silver ions is exhausted or, in other cases, where silver is made available it will be desirable that any materials, other than the
25 silver itself, which are simultaneously released should be physiologically harmless. In yet other cases, it may be necessary to ensure that the pH of the resulting solution does not fall outside defined limits.

30 Typically the soluble glasses used in this invention comprise phosphorus pentoxide (P_2O_5) as the principal glass-former, together with any one or more glass-modifying non-toxic materials such as sodium oxide (Na_2O), potassium oxide (K_2O), magnesium oxide (MgO) and calcium oxide (CaO). The
35 rate at which the silver-release glass dissolves in fluids

is determined by the glass composition, generally by the ratio of glass-modifier to glass-former and by the relative proportions of the glass-modifiers in the glass. By suitable adjustment of the glass composition, the

5 dissolution rates in water at 38°C ranging from substantially zero to 25mg/cm²/hour or more can be designed. The water-soluble glass is preferably a phosphate glass, and the silver may advantageously be introduced during manufacture as silver orthophosphate (Ag₃PO₄). The content

10 of silver and other constituents in the glass can vary in accordance with conditions of use and desired rates of release, the content of silver generally being up to 10% by weight.

15 The glass may be formed by a number of methods. It may simply be cast by conventional or centrifugal procedures, or it may be prepared via one or more stages of rod, fibre or tube drawing. Other preparation techniques include foamed glass or comminution of the glass followed by pressing and

20 sintering into a solid body. It may be presented for example as a solid body, a powder or granules of preselected size.

A preparation of this invention may comprise a composite

25 material containing one or more than one water-soluble glass composition. The anti-microbial properties of the preparation of the invention are due entirely to the bacteriostatic properties of silver ions.

30 The antimicrobial properties of the preparation of the invention were demonstrated by placing a section of silver-containing water-soluble glass, cut from a 4mm rod, in culture medium. Over a period of 36 hours the growth of Pseudomonas aeruginosa was inhibited. A similar result was

35 obtained when the culture medium was replaced with fluids

recovered after use in Continuous Ambulatory Peritoneal Dialysis (CAPD). The inhibition of bacterial growth by slow release of silver has a wide range of application in those treatment where fluid enters or leaves the body by natural processes or by routes introduced by surgical intervention.

One such example exists in CAPD where patients with renal failure receive regular exchanges of dialysis fluid introduced into the peritoneal cavity. Delivery is carried out under aseptic conditions from an individual bottle or plastics bag of sterile dialysis fluid via a resident catheter in the lower abdomen. Each time the circuit is broken there is a risk of infection both at the implant site and in the peritoneum which can lead to episodes of peritonitis and also to the required removal of the implanted catheter. The interposing of silver-release glass at the connector sites, through which liquid entering or leaving the peritoneal cavity flows, offers a barrier to bacterial invasion.

Similarly, with parenteral infusions involving individual cannulae and catheters the incorporation of an antimicrobial barrier in accordance with this invention will reduce the risk to the patient.

The antimicrobial action of silver is known. One of the most widely used silver-based pharmaceutical compositions is silver sulphadiazine which is commonly used, in the form of an ointment, for the treatment of burn wounds, which are particularly subject to contamination by colonising organisms, especially bacterial and fungi, by topical application. In contact with the wound the silver sulphadiazine dissociates into silver ions and sulphadiazine, both components possessing antibiotic

properties. The compound also exhibits some degree of slow or sustained release of the silver and sulphadiazine because of its relatively low aqueous solubility which, of course, retards the dissociation necessary for release of the antibiotic action. Silver nitrate and silver allantoinate are also used.

Embodiments of the present invention will now be described by way of example with reference to the accompanying drawings, in which:

Fig. 1 is a side view of apparatus of the present invention;

Figs. 2(a) and (b) are side views of different forms of the apparatus of the invention in use; and

Fig. 3 is a side sectional view of an alternative connection member of this invention.

Referring to Fig. 1, the apparatus of this embodiment of the invention comprises an indwelling urinary catheter 2 having inflatable balloon portions 4, 6 for maintaining the catheter in position in the urethra with the free end 8 in the bladder to collect urine through apertures 10, 12. At the outer end the catheter 2 terminates in a first portion 14 of a connector 16 whose second portion 18 leads to tubing 20 which enters a urine collection bottle 22. The bottle 22 has at its lower end remote from the tubing 20 a drain plug 24. The connection between the first and second portions 14, 18 of the connector represents a site of potential contamination by bacteria which can be introduced on releasing the connector 16, for example to change the bottle 22 and tubing 20.

The urine itself is contaminated and the bacteria can

reproduce in the bottle 22 as the urine collects in it. Thus when a nurse empties the bottle 22 through the drain plug 24 there is a risk of bacteria being transferred to the nurse. Further, bacteria in the bottle 22 may find their way along the tubing 20, connector 16 and catheter 2 into the patient's bladder, causing infection.

In order to prevent such infection by bacterial reproduction and transfer, the first portion 18 of the connector 16 has a peripheral recess 26 defined by spaced shoulders 28, 30, and a sleeve or lining 32 of water-soluble glass impregnated with silver is retained in the recess 26 to form part of the flow passageway for urine through the connector. Further, the bottle 22 contains a braided pouch 34 within which are held granules of the impregnated water-soluble glass, the pouch being tubular and closed at each end. The material of the pouch 34 is such that it contains interstices which allow urine to pass through but which are small enough to prevent the granules of the glass escaping.

In use the glass sleeve 32 and the glass in the pouch 34 act as a bacteriostat preventing an increase in the number of bacteria in the urine itself and of bacteria introduced in the event of the connector 16 being opened, for example to change the bottle 22. This occurs by virtue of the gradual dissolution of the glass, releasing the silver with its bacteriostatic properties over a prolonged period. The composition of the glass determines the rate of silver release.

Fig. 2(a) illustrates the use of a connector 16, which is of similar construction to that shown in Fig. 1, in peritoneal dialysis in which fluid passes from a reservoir 38 into the peritoneum of the patient. In this case the fluid itself is sterile so the reservoir 38 need not contain a pouch 34

as in Fig. 1, but the sleeve 32 is required in the connector 16 to deal with bacteria which may be introduced when the connector is opened in order to replace the reservoir 38 when empty. Fig. 2(b) illustrates the apparatus in post-surgical drainage, in which suction is applied through a line 40 to the patient to draw fluid from the operation site into a collection bottle 42. Again, the connector 16 is of similar construction to that of Fig. 1 and includes the silver-impregnated sleeve 32.

10

Referring now to Fig. 3, the connector 16 has first and second portions 14, 18 having an ingot 44 of silver-contaminated water-soluble glass between them. The ingot 44 is in the form of a solid sleeve 46 having an annular flange 48 at one end to bear against an end face of the first portion 14 and a corresponding shoulder 47 on the second portion 18. The first and second portions 14, 18 each have a fitting 49, 50 for receiving an end portion of rubber tubing. The sleeve 46 fits within the first portion 14 so as to contact fluid passing through the connector 16.

In the connector of Fig. 3, the ingot 44 is made by mixing together 35 mole % of NaH_2PO_4 , 15 mole % of CaHPO_4 and 50 mole % of P_2O_5 , heating the mixture at 1050°C for 20 minutes, and cooling and grinding the glass thus obtained until it forms a powder. This powder is then weighed and up to 10% by weight of silver orthophosphate (Ag_3PO_4) is added and mixed in. The mixture is then heated to 1050°C to produce a homogeneous impregnated water-soluble glass, cast into shape and annealed.

The granulated form of the glass provided in the pouch 34 of Fig. 1 can also be made in this way, with a final granulation stage instead of casting.

Alternatively the silver orthophosphate can be included in the original mix to allow a single heating stage.

5 It has been found that if the silver-impregnated water-soluble glass used in these embodiments of the invention is heated directly at its surface after its manufacture, in a manner that creates a rapid temperature gradient through the material, elemental silver forms at the surface in a fine layer which in use provides an initial increased rate
10 of dissolution of the silver into the fluid until the surface layer has all dissolved, after which the glass dissolves as normal with a slower rate of release of silver. In producing this effect it is important that the heating is not sustained after the formation of the silver surface
15 layer as the glass otherwise devitrifies and the release rate of the silver becomes unpredictable.

Experiments using apparatus of the invention will now be described by way of example.

20 The silver-impregnated water-soluble glass was produced in two forms which would enable its incorporation into the urinary catheter collection system of Fig. 1 but using the connector shown in Fig. 3:

25 1. A silver-impregnated glass ingot inside a plastic connector which would be situated between the distal end of the catheter and the proximal end of the urine collection bag tubing. The reason for siting the silver glass here is
30 that many episodes of urinary tract infection in catheterised patients are thought to result from contamination of the catheter/bag junction when the collection bag is disconnected and reconnected.

35 2. A porous plastic pouch containing small granules of

silver-impregnated glass which would be situated inside the collection bag releasing silver ions into the collected urine. This would reduce the numbers of bacteria present in the collection bag which is thought to be a potential source of cross-infection in wards where there are several catheterised patients.

Experiment 1

Brain heart infusion broth containing small pellets of silver-impregnated glass were inoculated with small numbers of different test organisms and the broths incubated at 37°C overnight. Test organisms used were

Escherichia coli
Pseudomonas aeruginosa
Proteus mirabilis
Klebsiella sp
Staphylococcus aureus
Staphylococcus epidermidis

The broths were subcultured after 48 hours to assess whether bacterial growth had been inhibited or not. Control cultures were also set up which did not contain silver-impregnated glass pellets.

Experiment 2

Pooled samples of urine containing varying numbers of bacteria ranging from 1×10^5 to 1×10^7 organisms per ml of urine were run through the silver-impregnated glass ingot containing connector at the rate of 1 ml per minute (the approximate rate at which urine flows through a urinary catheter) for 2 hours. The number of organisms present in the urine before and after flowing through the connector and

after incubation of the collected urine at room temperature for 24 hours were estimated. These were compared to the numbers of organisms present in similar samples of the pooled urine which had not been passed through the connector.

Experiment 3

Filtered (sterile) urine was run through the silver-impregnated glass connector at the rate of 1 ml per minute for 2 hours as before. The connector was then artificially contaminated with 1×10^6 organisms of E. coli and sterile urine run through the connector for a further 1 hour. This was to simulate contamination of the connector during changing of the collection bag. The numbers of organisms present in the collected urine was estimated immediately after collection (Time 0) and after 24, 48, 72, and 96 hours' incubation at room temperature.

This experiment was also carried out using nutrient broth instead of sterile urine (when urine was unavailable).

Experiment 4

Sterile urine was allowed to flow through the silver-impregnated glass connector at the rate of 1 ml per minute for 24 hours. Several samples were taken during this time for silver estimation in order to gain a picture of the rate of silver release into the collected urine.

Experiment 5

Filtered (sterile) urine was collected in a container containing silver-impregnated water-soluble glass granules in a braided plastic pouch. This urine was then

artificially contaminated with a known number of organisms of E. coli and the collected urine incubated at room temperature for 4 days, the numbers of organisms present in the urine being estimated daily.

5

Results

Preliminary experiments which assessed the ability of silver-impregnated glass to inhibit the growth of different types of bacteria showed that the glass pellets inhibited the growth of all types of bacteria except the Proteus mirabilis.

10

In Experiment 2, passing the urine through the connector did not immediately reduce the numbers of organisms present in the urine, but after 24 hours' incubation there was approximately a ten-fold reduction in the numbers of organisms in the urine which had been passed through the connector when compared with the control urine.

15

20

When sterile urine or nutrient broth was used and the connector artificially contaminated with E. coli, the numbers of organisms in the control urine had significantly multiplied after 24 hours' incubation, but the test urine which had been passed through the connector showed very small numbers of organisms present after 24 and 48 hours and regrowth of the E. coli did not occur until after 72 or 96 hours' incubation.

25

The preliminary results of the experiments assessing the use of the plastic pouch containing silver-impregnated glass granules to inhibit organism growth gave positive results.

30

Both the glass-containing connector and the plastic pouch containing glass granules released enough silver to inhibit

35

15.

the growth of bacteria and can be incorporated into urinary collection systems in order to reduce the risk of urinary tract infection in catheterised patients.

- 5 In the above Experiments the ingot contained in the connector comprised 35 mole % NaH_2PO_4 , 15 mole % CaHPO_4 and 50 mole % P_2O_5 , and 10% by weight of silver. This resulted in a rate of release of silver of 1 mg per cm^2 per hour.
- 10 The granules in the plastic pouch comprised 25 mole % NaH_2PO_4 , 25 mole % CaHPO_4 and 50 mole % P_2O_5 , with 5% by weight of silver. The silver release rate was 0.6 mg per cm^2 per hour.
- 15 In general, an increase in the amount of sodium present in the glass increases the rate of dissolution and therefore of silver release when the P_2O_5 content remains constant.

Modifications and improvements may be made without departing
20 from the scope of the invention.

CLAIMS

1. Apparatus for antimicrobial use in passage of fluid to or from a living body, the apparatus comprising a conduit
5 for insertion into the body, a reservoir for fluid and a connector member for connecting said conduit to said reservoir external of the body, wherein said connector member includes a water-soluble glass impregnated with elemental silver or a compound of silver, said water-soluble
10 glass defining at least a part of a passageway for fluid to flow between the reservoir and the conduit.
2. Apparatus according to Claim 1, wherein the connector member comprises a first portion having an end adapted for
15 connection with said conduit and a second portion having an end adapted for connection with said reservoir, the first and second portions being releasably secured together to define a fluid passageway between the reservoir and the conduit and at least one of the first and second portions
20 having an internal lining of said impregnated water-soluble glass.
3. Apparatus according to Claim 2, wherein at least one of the first and second portions of the connector member has a
25 pair of spaced shoulders between which said lining of impregnated water-soluble glass is retained.
4. Apparatus according to Claim 1, 2 or 3, wherein the connector member comprises tubing having said impregnated
30 water-soluble glass dispersed therein.
5. Apparatus according to any one of the preceding Claims, wherein said reservoir contains water-soluble glass impregnated with elemental silver or a compound of silver.

6. Apparatus according to Claim 5, wherein the impregnated water-soluble glass in the reservoir is disposed within an apertured container.
- 5 7. Apparatus according to Claim 6, wherein the container is in the form of a flexible braided pouch having interstices through which liquid can pass.
8. Apparatus according to any one of the preceding Claims,
10 wherein the impregnated water-soluble glass is granular.
9. Apparatus according to any one of the preceding Claims, wherein the impregnated water-soluble glass has a surface layer of elemental silver.
- 15 10. A connector member having an inlet and an outlet and having walling defining a through passageway for flow of liquid from the inlet to the outlet, at least a part of said walling being formed of water-soluble glass impregnated with
20 elemental silver or a compound of silver.

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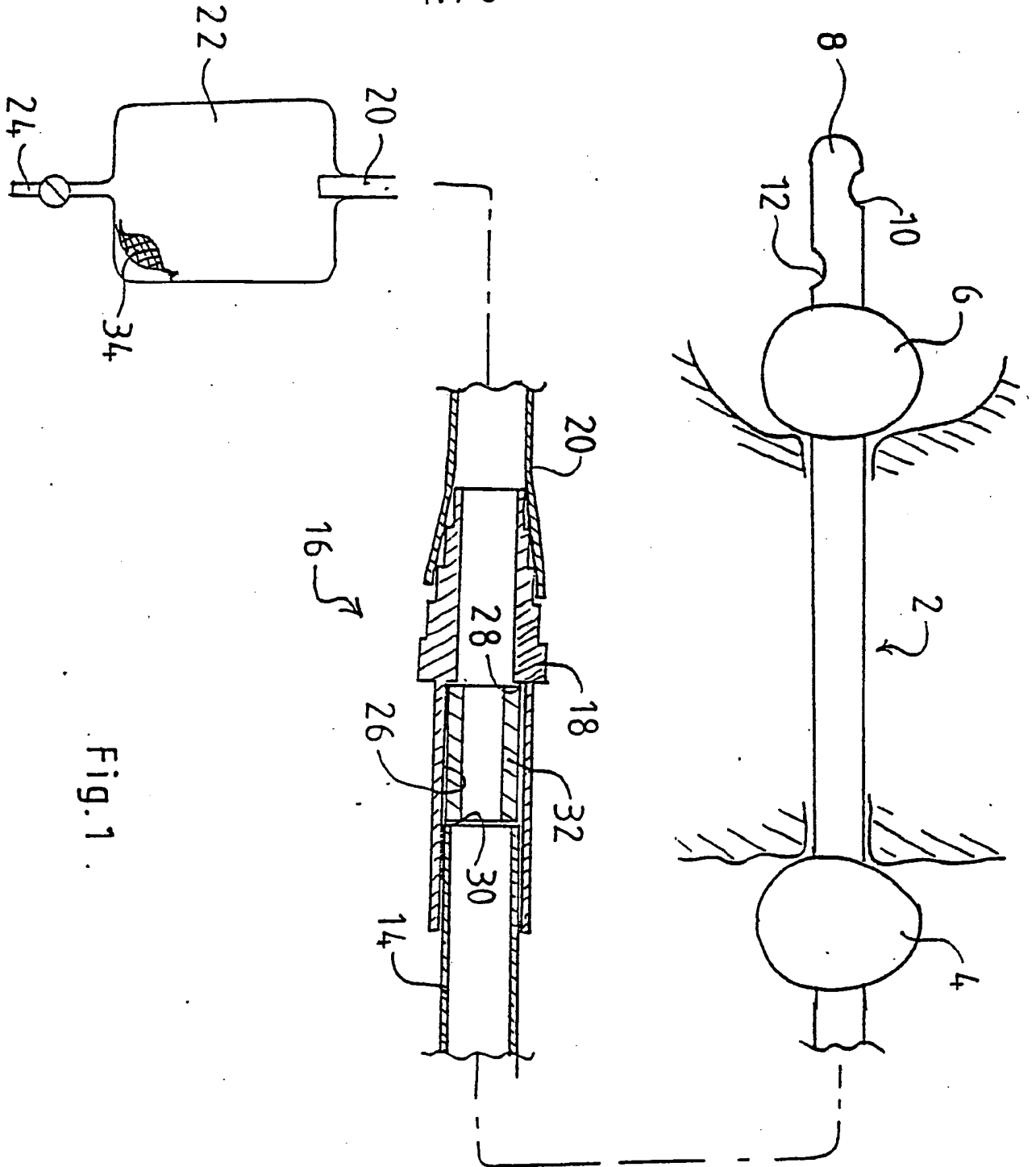


Fig. 1

2 / 3

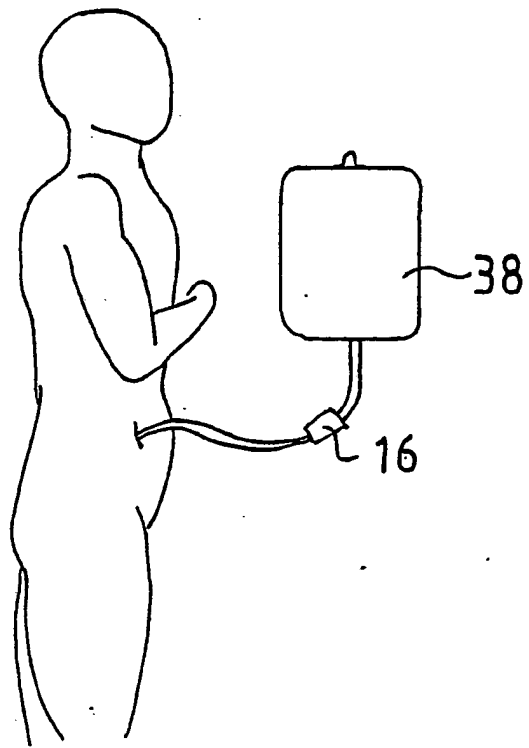


Fig. 2a

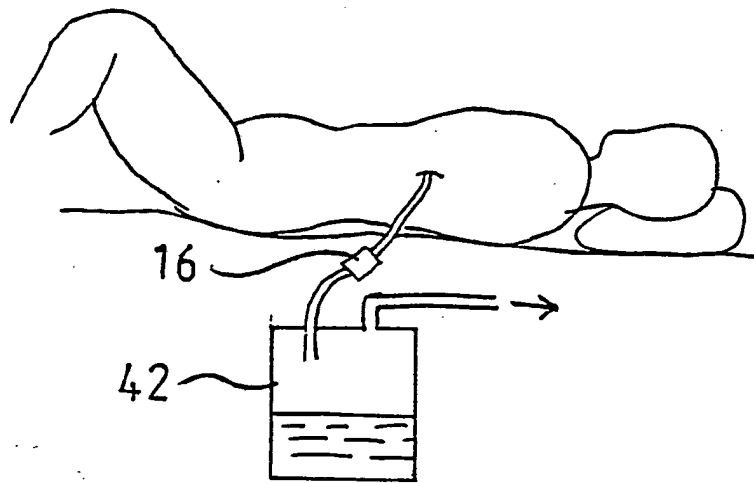


Fig. 2b

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 88/00701

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁴ : A 61 M 5/00; A 61 M 31/00; A 61 L 2/16																							
II. FIELDS SEARCHED <div style="text-align: right; font-size: small;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border: none;"> <tr> <td style="width: 25%; border: none;">Classification System</td> <td style="border: none;">Classification Symbols</td> </tr> <tr> <td style="border: none; vertical-align: top;">IPC⁴</td> <td style="border: none; vertical-align: top;">A 61 M; A 61 L; C 03 C</td> </tr> </table> <div style="text-align: center; font-size: x-small; margin-top: 5px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸</div>			Classification System	Classification Symbols	IPC ⁴	A 61 M; A 61 L; C 03 C																	
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III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table border="1" style="width: 100%; border-collapse: collapse; font-size: x-small;"> <thead> <tr> <th style="width: 10%;">Category ⁹</th> <th style="width: 70%;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 20%;">Relevant to Claim No. ¹³</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>FR, A, 2506162 (SOCIETE DE MATERIELS ANNEXES DE DIALYSE SMAD) 26 November 1982 see figures 1,2 --</td> <td style="text-align: center; vertical-align: top;">1</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>US, A, 4354490 (ROGERS) 19 October 1982 see claim 1 --</td> <td style="text-align: center; vertical-align: top;">1</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>WO, A, 85/01210 (UNIVERSITY OF STRATHCLYDE) 28 March 1985 see claim 3 --</td> <td style="text-align: center; vertical-align: top;">1</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>EP, A, 0140538 (STC PLC) 8 May 1985 see claims 1,11 & GB, A, 2146531 (cited in the application) --</td> <td style="text-align: center; vertical-align: top;">1,8</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>EP, A, 0042219 (ITT) 23 December 1981 see claims 1,5 & GB, A, 2077585, GB, A, 2079152 (cited in the application) --</td> <td style="text-align: center; vertical-align: top;">1</td> </tr> <tr> <td colspan="3" style="text-align: right; padding-right: 10px;">./.</td> </tr> </tbody> </table> <div style="font-size: x-small; margin-top: 10px;"> <div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p>* Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 48%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div> </div>			Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	A	FR, A, 2506162 (SOCIETE DE MATERIELS ANNEXES DE DIALYSE SMAD) 26 November 1982 see figures 1,2 --	1	A	US, A, 4354490 (ROGERS) 19 October 1982 see claim 1 --	1	A	WO, A, 85/01210 (UNIVERSITY OF STRATHCLYDE) 28 March 1985 see claim 3 --	1	A	EP, A, 0140538 (STC PLC) 8 May 1985 see claims 1,11 & GB, A, 2146531 (cited in the application) --	1,8	A	EP, A, 0042219 (ITT) 23 December 1981 see claims 1,5 & GB, A, 2077585, GB, A, 2079152 (cited in the application) --	1	./.		
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A	WO, A, 85/01210 (UNIVERSITY OF STRATHCLYDE) 28 March 1985 see claim 3 --	1																					
A	EP, A, 0140538 (STC PLC) 8 May 1985 see claims 1,11 & GB, A, 2146531 (cited in the application) --	1,8																					
A	EP, A, 0042219 (ITT) 23 December 1981 see claims 1,5 & GB, A, 2077585, GB, A, 2079152 (cited in the application) --	1																					
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IV. CERTIFICATION <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> Date of the Actual Completion of the International Search 22nd November 1988 International Searching Authority EUROPEAN PATENT OFFICE </td> <td style="width: 50%; border: none; vertical-align: top;"> Date of Mailing of this International Search Report <div style="text-align: center; font-size: large; font-weight: bold;">12 DEC 1988</div> Signature of Authorized Officer <div style="text-align: center;"> P.C.G. VAN DER PUTTEN </div> </td> </tr> </table>			Date of the Actual Completion of the International Search 22nd November 1988 International Searching Authority EUROPEAN PATENT OFFICE	Date of Mailing of this International Search Report <div style="text-align: center; font-size: large; font-weight: bold;">12 DEC 1988</div> Signature of Authorized Officer <div style="text-align: center;"> P.C.G. VAN DER PUTTEN </div>																			
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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	EP, A, 0059694 (AB HÄSSLE) 8 September 1982 see claim 1; figure 6 -----	1

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

GB 8800701

SA 24108

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 05/12/88. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A- 2506162	26-11-82	None	
US-A- 4354490	19-10-82	US-A- 4551146 US-A- 4655762	05-11-85 07-04-87
WO-A- 8501210	28-03-85	EP-A- 0155288	25-09-85
EP-A- 0140538	08-05-85	AU-A- 3278584 GB-A, B 2146531 JP-A- 60155110 US-A- 4587267 AU-B- 567968 CA-A- 1239545	21-03-85 24-04-85 15-08-85 06-05-86 10-12-87 26-07-88
EP-A- 0042219	23-12-81	GB-A- 2077585 GB-A- 2077586 GB-A, B 2079152 JP-A- 57029358 CA-A- 1167345 US-A- 4449981 AU-B- 552361 AU-A- 7142281	23-12-81 23-12-81 20-01-82 17-02-82 15-05-84 22-05-84 29-05-86 17-12-81
EP-A- 0059694	08-09-82	JP-A- 57156773 SE-A- 8101247 AU-A- 8075882 AU-B- 547298 CA-A- 1207622	28-09-82 27-08-82 02-09-82 17-10-85 15-07-86